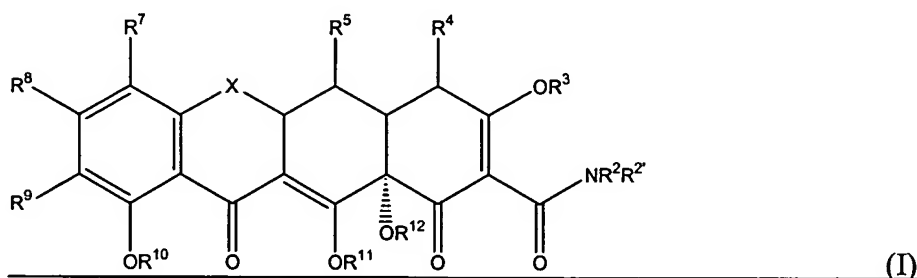


### AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions of the claims and listing of the claims in the application:

1. **(Currently Amended)** A method for treating or preventing malaria in a subject, comprising administering to said subject an effective amount of a substituted tetracycline compound, of formula I:



wherein:

X is CR<sup>6'</sup>R<sup>6</sup>;

R<sup>2</sup>, R<sup>2'</sup>, R<sup>4'</sup>, and R<sup>4''</sup> are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R<sup>4</sup> is NR<sup>4'</sup>R<sup>4''</sup>, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R<sup>3</sup>, R<sup>11</sup> and R<sup>12</sup> are each hydrogen, or a pro-drug moiety;

R<sup>10</sup> is hydrogen, a prodrug moiety, or linked to R<sup>9</sup> to form a ring;

R<sup>5</sup> is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R<sup>6</sup> and R<sup>6'</sup> are independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R<sup>7</sup> is a malaria interacting moiety;

R<sup>9</sup> is hydrogen;

R<sup>8</sup> is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and pharmaceutically acceptable salts thereof, such that malaria is treated or prevented in said subject.

2. (Cancelled)

3. (Currently Amended) The method of claim 2 ~~1~~, wherein  $R^2$ ,  $R^{2'}$ ,  $R^3$ ,  $R^8$ ,  $R^{10}$ ,  $R^{11}$ , and  $R^{12}$  are hydrogen;  $R^4$  is  $NR^{4'}R^{4''}$ ;  $R^{4'}$  and  $R^{4''}$  are alkyl, and X is  $CR^6R^{6'}$ .

4. (Currently Amended) The method of claim 3, wherein  $R^5$ ,  $R^6$ , and  $R^{6'}$  are each hydrogen, ~~and  $R^7$  is dimethylamino.~~

5. (Currently Amended) The method of claim 3, wherein  $R^5$  is hydroxy or a prodrug moiety,  $R^6$  is methyl, and  $R^{6'}$  is hydrogen ~~and  $R^7$  is hydrogen.~~

6.-25. (Cancelled)

26. (Original) The method of claim 3, wherein  $R^7$  is a malaria interacting moiety.

27. (Original) The method of claim 26, wherein  $R^7$  comprises 4 to 20 carbon, nitrogen, sulfur, or oxygen atoms.

28. (Original) The method of claim 26, wherein said malaria interacting moiety comprises an aryl group.

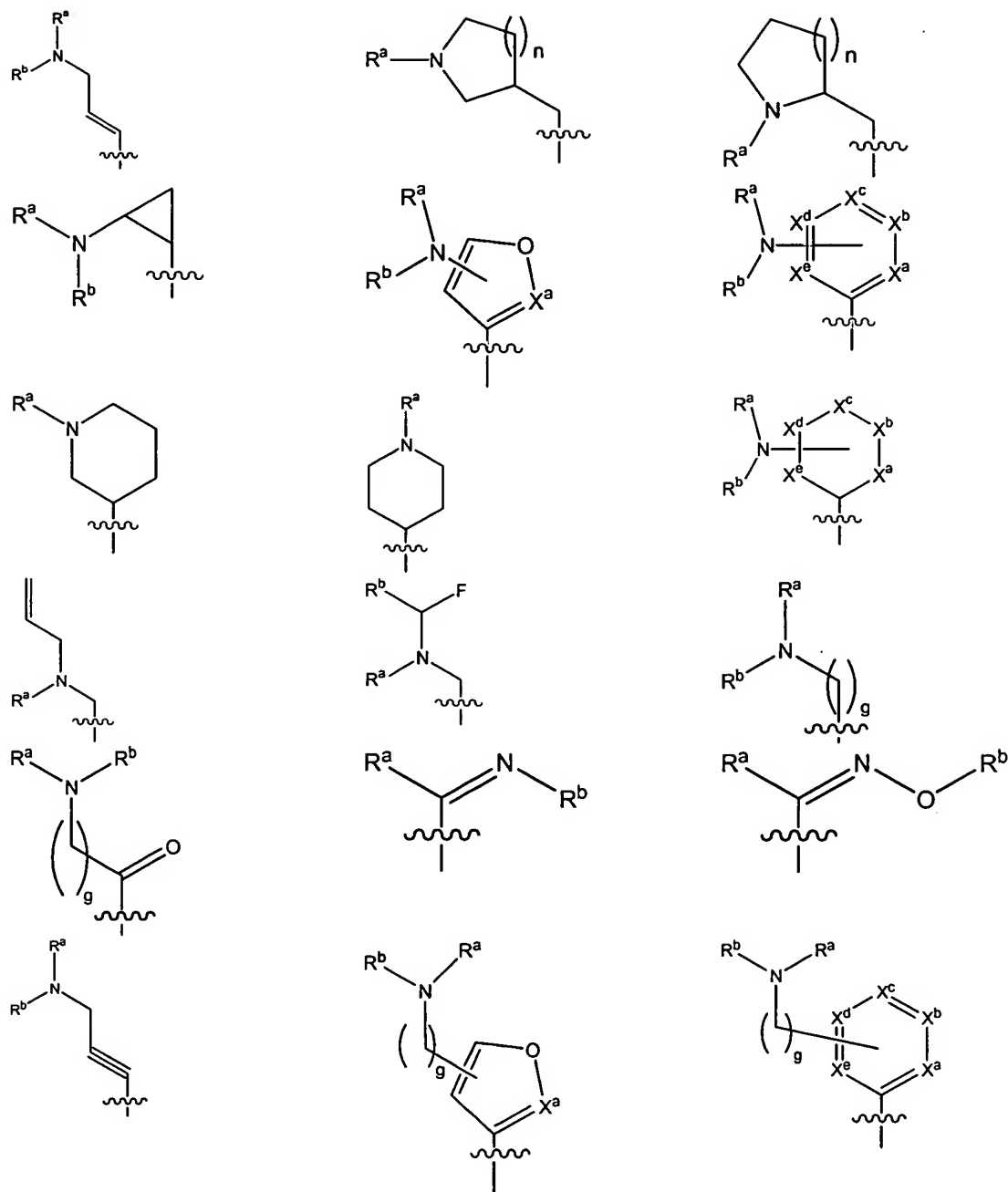
29. (Original) The method of claim 28, wherein said aryl group is substituted or unsubstituted phenyl.

30. (Original) The method of claim 29, wherein said phenyl group is substituted with halogen, alkoxy, amino, acyl, alkyl, nitro, formyl, amido, alkyl, alkenyl, alkynyl, or aryl.

31. (Original) The method of claim 30, wherein said alkoxy group is methoxy, ethoxy, propoxy, methylene dioxy, or ethylene dioxy.

32. (Original) The method of claim 30, where said alkyl group is substituted or substituted methyl, ethyl, propyl, butyl or pentyl.

33. **(Original)** The method of claim 32, wherein said alkyl group is substituted with an amino, carbocyclic or heterocyclic group.
34. **(Original)** The method of claim 30, wherein said acyl group is acetyl.
35. **(Original)** The method of claim 28, wherein said aryl group is substituted or unsubstituted heteroaryl.
36. **(Original)** The method of claim 35, wherein said heteroaryl is thienyl, imidazolyl, pyrrolyl, pyridinyl, furanyl, pyrimidinyl, or benzofuranyl.
37. **(Original)** The method of claim 26, wherein said malaria interacting moiety is substituted or unsubstituted alkynyl.
38. **(Original)** The method of claim 37, wherein said alkynyl is substituted with a substituted or unsubstituted aryl group.
39. **(Original)** The method of claim 26, wherein said malaria interacting moiety is alkyl or alkenyl.
40. **(Original)** The method of claim 26, wherein said malaria interacting moiety is C<sub>1</sub>-C<sub>15</sub>.
41. **(Original)** The method of claim 26, wherein said malaria interacting moiety is substituted carbonyl.
42. **(Original)** The method of claim 26, wherein said malaria interacting moiety comprises an ionizable nitrogen atom.
43. **(Original)** The method of claim 26, wherein said malaria interacting moiety is selected from the group consisting of:



wherein:

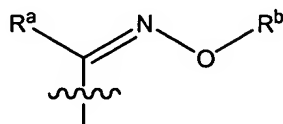
$R^a$  and  $R^b$  are each independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, or heterocyclic;

$g$  is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20;

$n$  is 0, 1, 2, or 3; and

$X^a$ ,  $X^b$ ,  $X^c$ ,  $X^d$ , and  $X^e$  are each independently optionally substituted carbon, oxygen, nitrogen, or sulfur.

44. (Original) The method of claim 43, wherein said malaria interacting moiety is

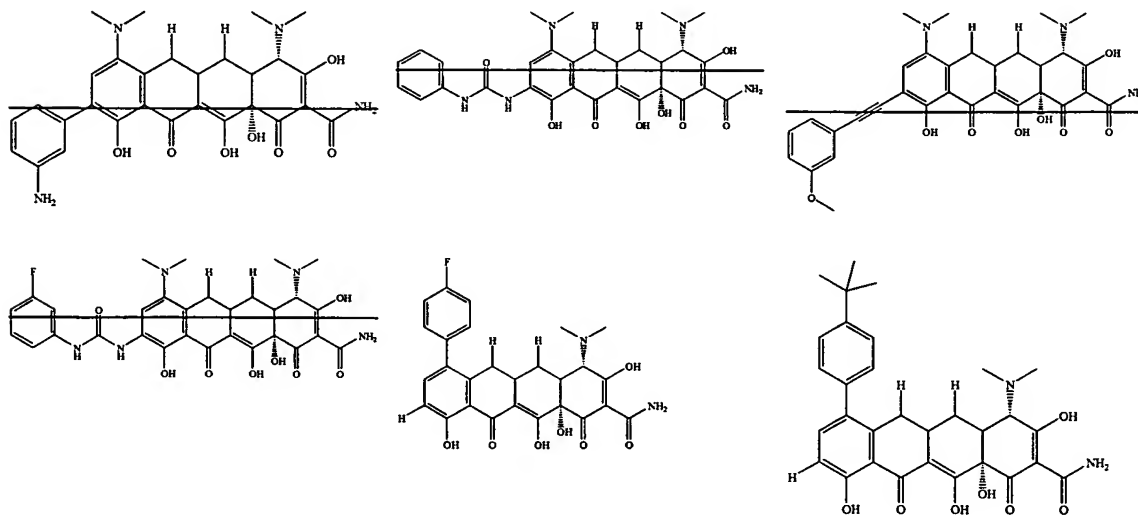


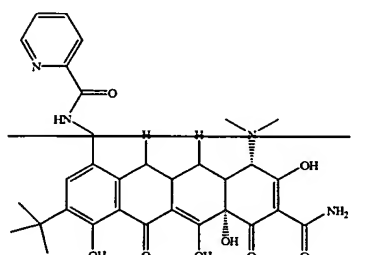
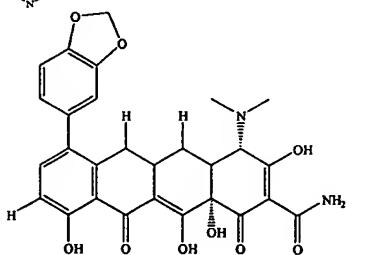
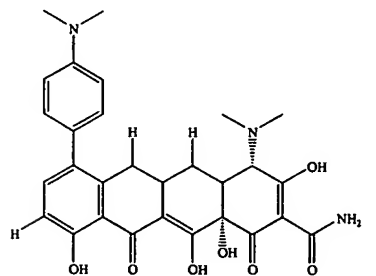
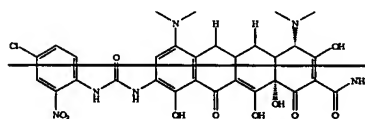
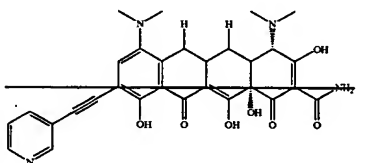
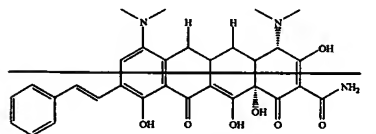
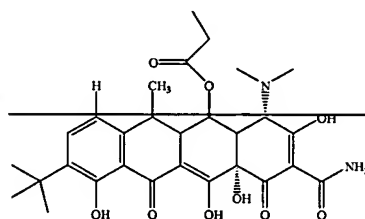
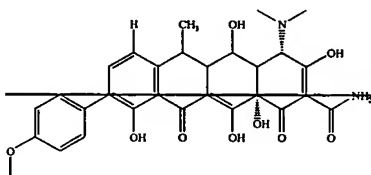
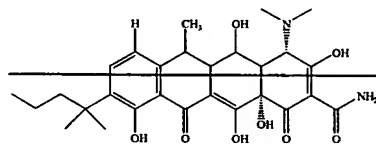
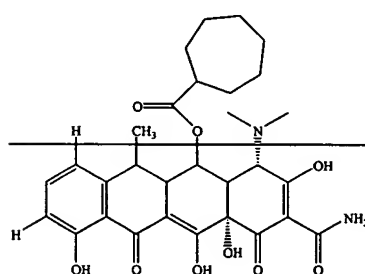
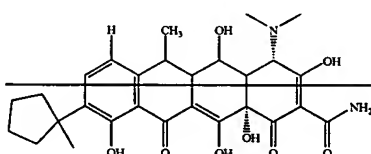
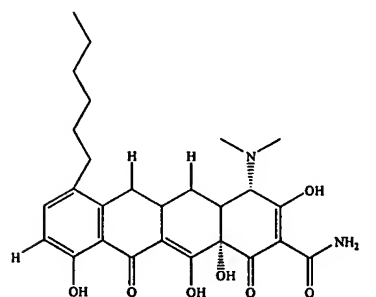
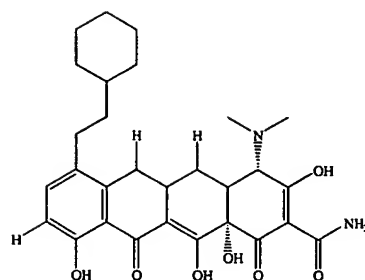
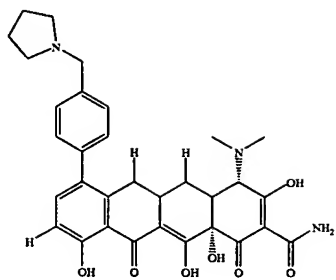
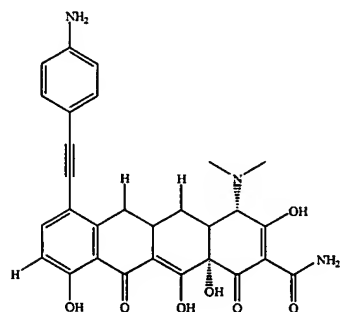
45. (Original) The method of claim 44, wherein  $\text{R}^a$  and  $\text{R}^b$  are each alkyl.

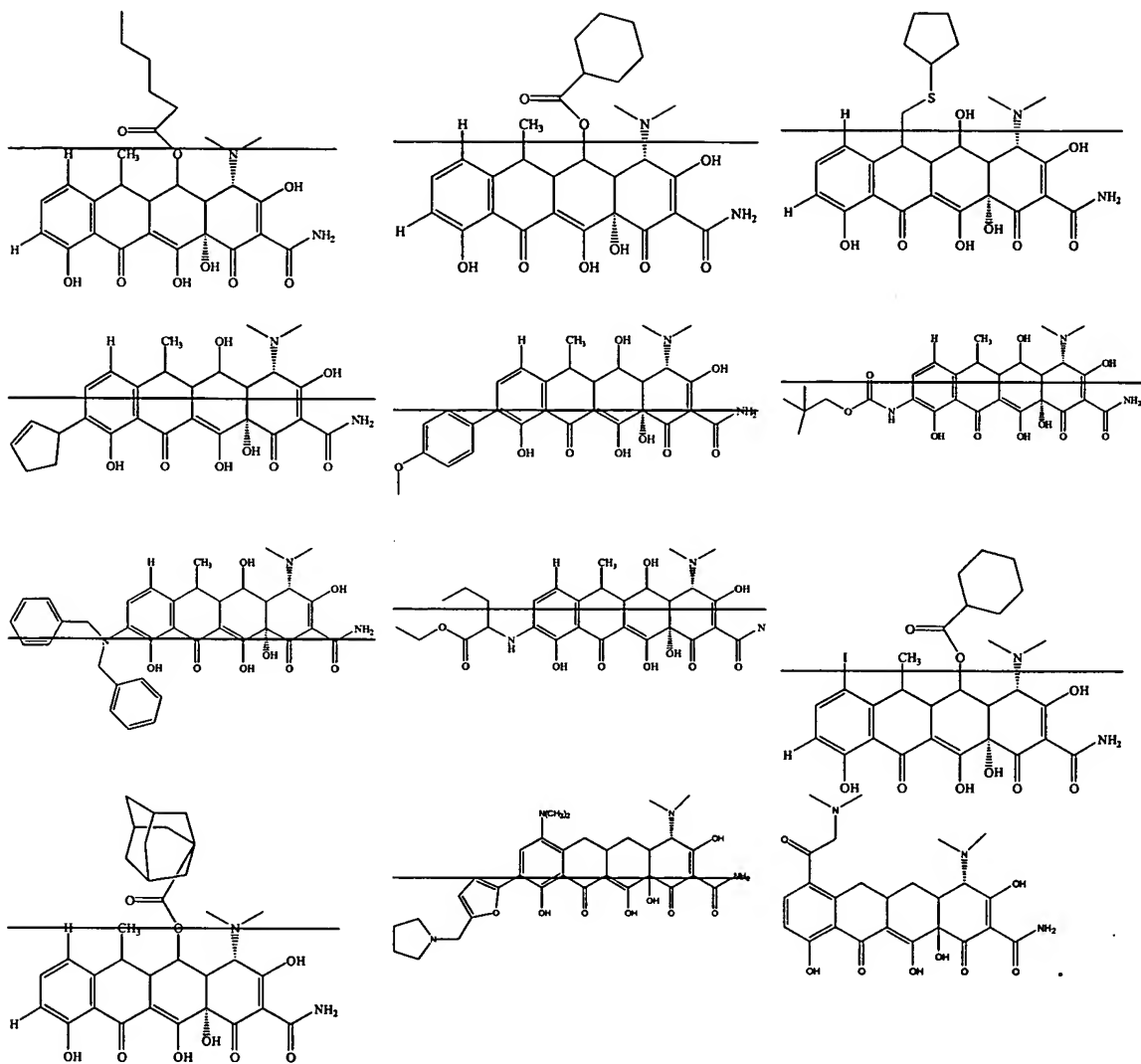
46. (Cancelled)

47. (Cancelled)

48. (Currently Amended) The method of claim 2 1, wherein said compound is selected from the group consisting of:

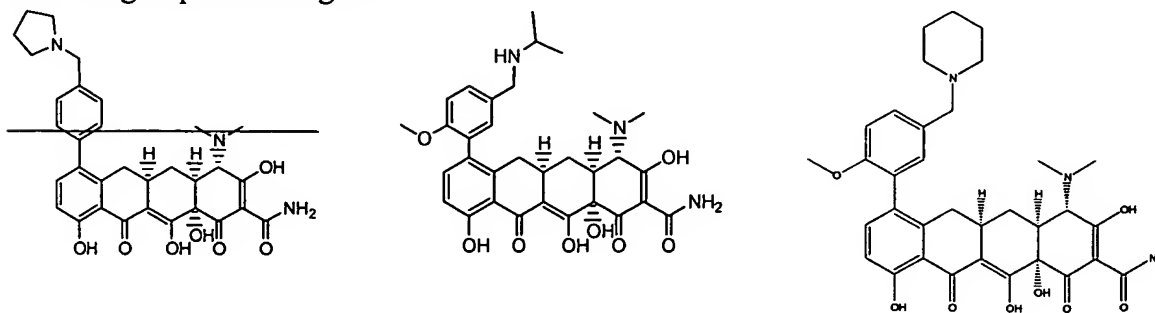


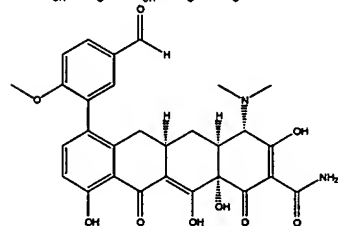
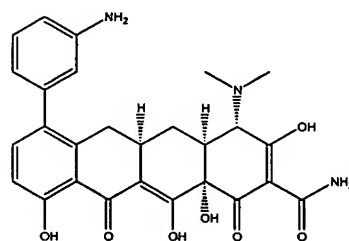
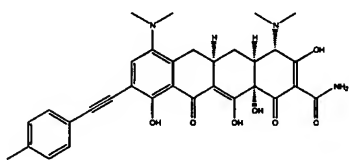
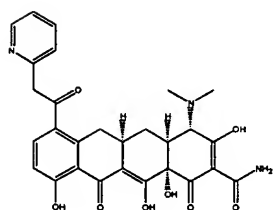
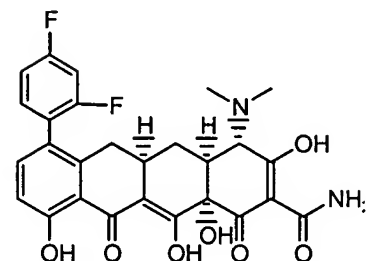
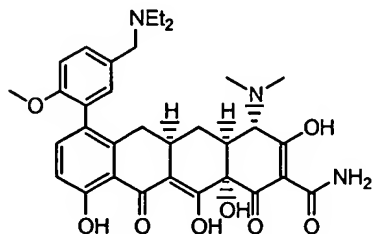
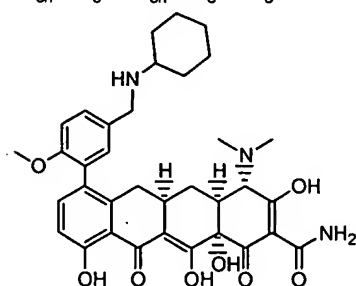
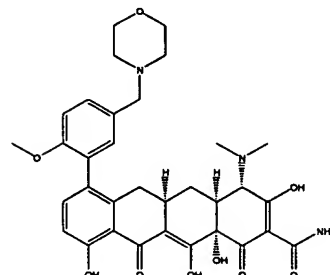
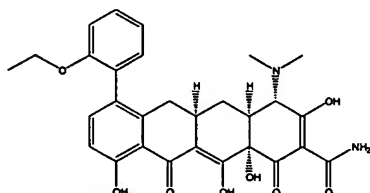
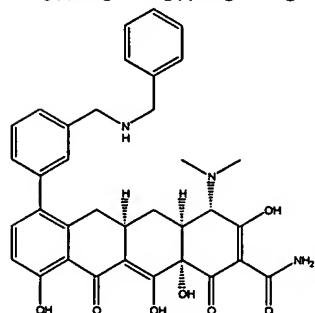
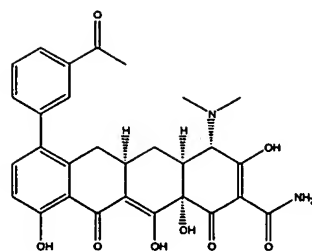
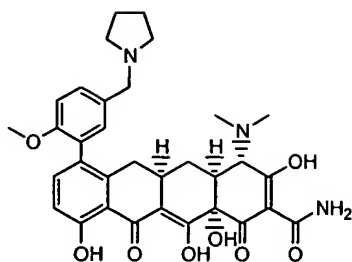
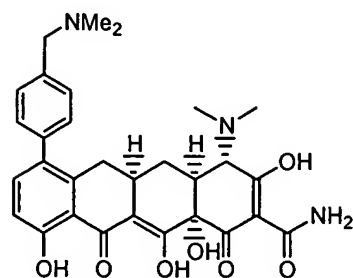




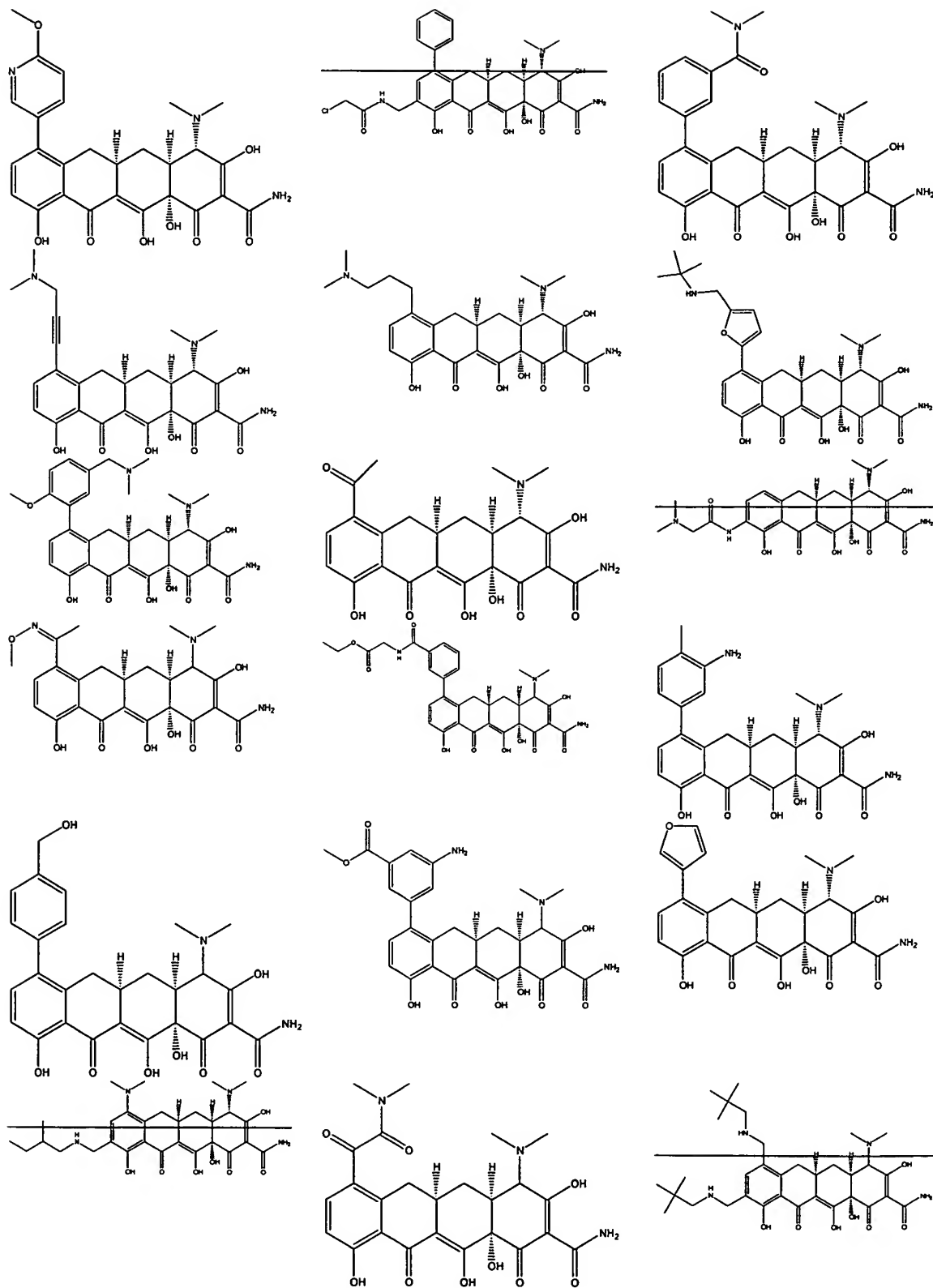
49. (Currently Amended)  
from the group consisting of:

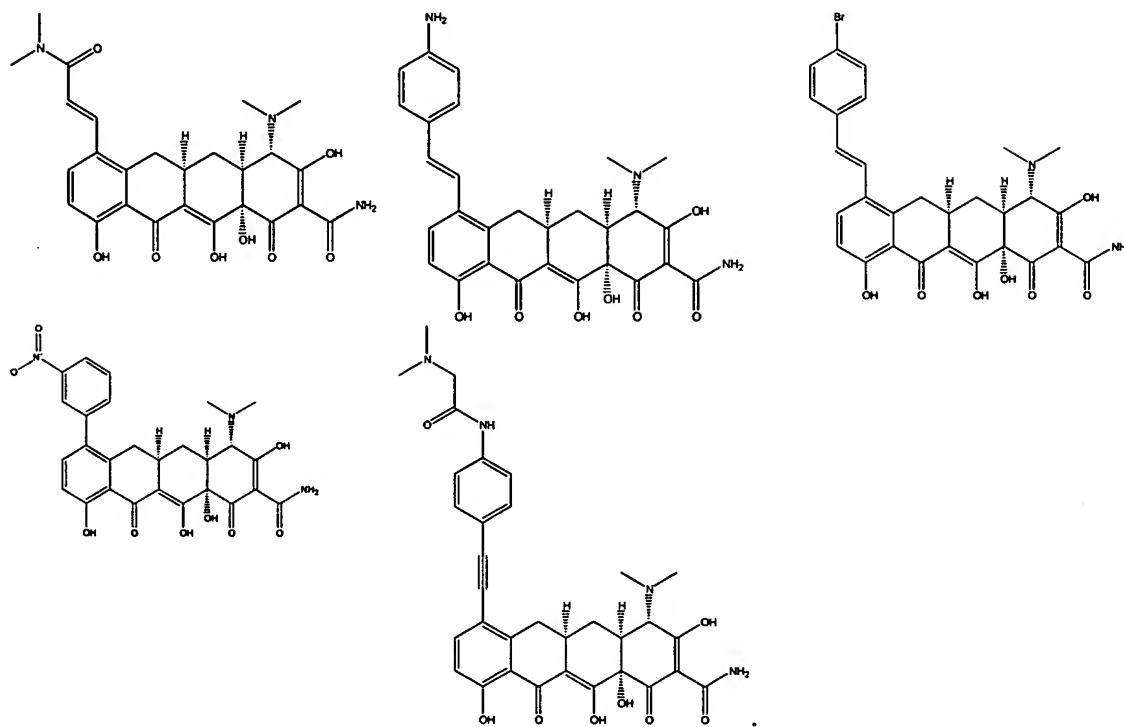
The method of claim 2 1, wherein said compound is selected











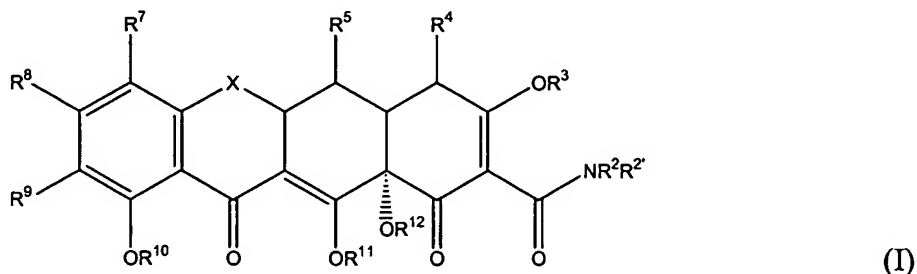
50. **(Currently Amended)** The method of claim 2 1, wherein said compound is a compound shown in Table 1 or Table 2.
51. **(Original)** The method of claim 1, wherein said subject is a human.
52. **(Original)** The method of claim 1, wherein said substituted tetracycline compound is has anti-microbial gram positive activity.
53. **(Original)** The method of claim 52, wherein said anti-microbial gram positive activity is greater than about 0.05  $\mu\text{g/ml}$ .
54. **(Original)** The method of claim 53, wherein said anti-microbial gram positive activity is greater than about 5  $\mu\text{g/ml}$ .
55. **(Original)** The method of claim 1, wherein said substituted tetracycline compound in non-antibacterial.

56. **(Original)** The method of claim 1, wherein said substituted tetracycline compound has a cytotoxicity of 25 µg/ml or greater.
57. **(Original)** The method of claim 1, wherein said substituted tetracycline compound has a MIC of 150 nM or less.
58. **(Original)** The method of claim 57, wherein said substituted tetracycline compound has a MIC of 50 nM or less.
59. **(Original)** The method of claim 58, wherein said substituted tetracycline compound has a MIC of 10 nM or less.
60. **(Original)** The method of claim 59, wherein said substituted tetracycline compound has an MIC or 5 nM or less.
61. **(Original)** The method of claim 1, wherein said malaria is caused by a plasmodium protozoan selected from the group consisting of: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*.
62. **(Original)** The method of claim 1, wherein said malaria is resistant to one or more anti-malarial compounds selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, proguanil, and 1,16-hexadecamethylenebis(N-methylpyrrolidinium) dibromide.
63. **(Original)** The method of claim 1, further comprising administering a supplementary compound.
64. **(Original)** The method of claim 63, wherein said supplementary compound treats a symptom selected from the group consisting of: headache, malaise, anemia, splenomegaly, and fever.

65. **(Original)** The method of claim 64, wherein said supplementary compound is an anti-malarial compound.

66. **(Original)** The method of claim 65, wherein said anti-malarial compound is selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide, and combinations thereof.

67. **(Currently Amended)** A method for increasing the antimalarial activity of an antimalarial compound, comprising administering said antimalarial compound in combination with an effective amount of a substituted tetracycline compound, such that the antimalarial activity of said antimalarial compound is increased, wherein said tetracycline compound is of formula I:



wherein:

X is CR<sup>6'</sup>R<sup>6</sup>;

R<sup>2</sup>, R<sup>2'</sup>, R<sup>4'</sup>, and R<sup>4''</sup> are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R<sup>4</sup> is NR<sup>4'</sup>R<sup>4''</sup>, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R<sup>3</sup>, R<sup>11</sup> and R<sup>12</sup> are each hydrogen, or a pro-drug moiety;

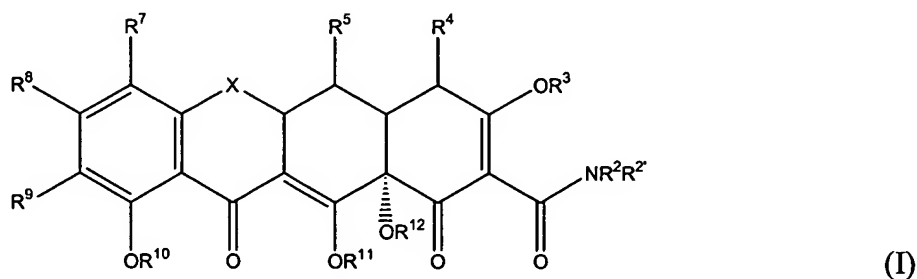
R<sup>10</sup> is hydrogen, a prodrug moiety, or linked to R<sup>9</sup> to form a ring;

R<sup>5</sup> is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

~~with the proviso that the compound of formula I is not oxytetracycline, demeclocycline, doxycycline, chlorotetracycline, minocycline, or tetracycline; and pharmaceutically acceptable salts thereof.~~

68. **(Original)** The method of claim 67, wherein said anti-malarial compound is selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide, and combinations thereof.

69. **(Currently Amended)** A method for preventing malaria in a mammal, comprising administering to said mammal an effective amount of a substituted tetracycline compound, such that malaria is prevented in said mammal, wherein said tetracycline compound is of formula I:



$R^4$  is  $NR^{4'}R^{4''}$ , alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

$R^3$ ,  $R^{11}$  and  $R^{12}$  are each hydrogen, or a pro-drug moiety;

$R^{10}$  is hydrogen, a prodrug moiety, or linked to  $R^9$  to form a ring;

$R^5$  is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

$R^6$  and  $R^{6'}$  are independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

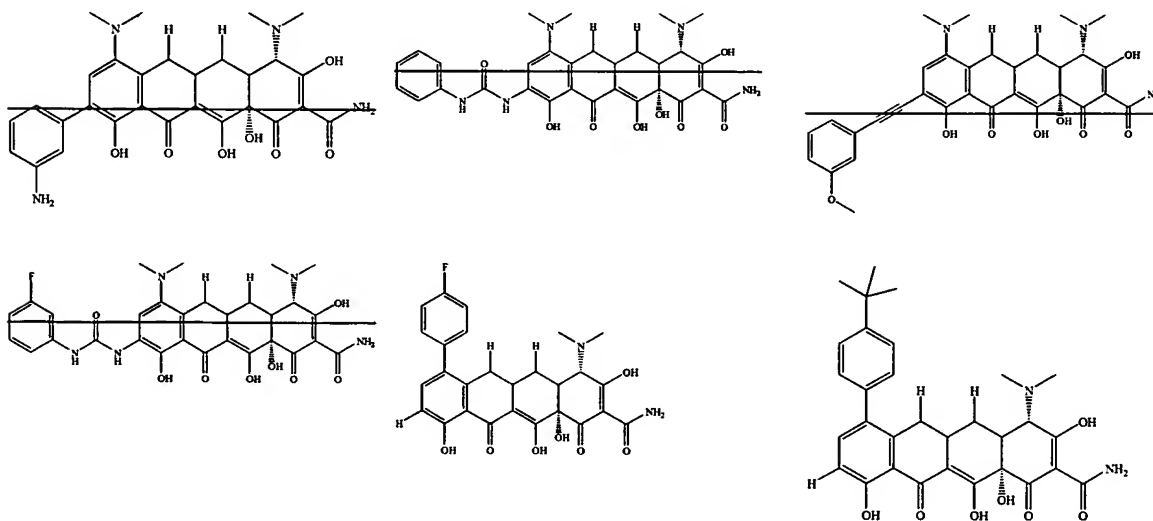
$R^7$  is ~~hydrogen, alkylamino, dialkylamino, or~~ a malaria interacting moiety;

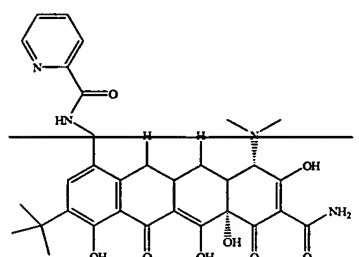
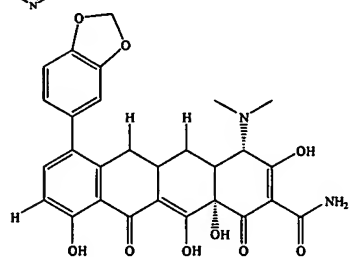
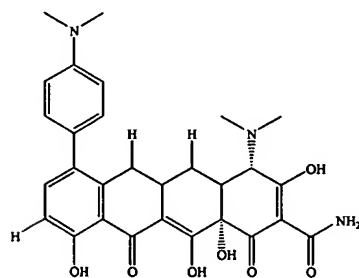
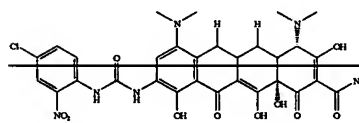
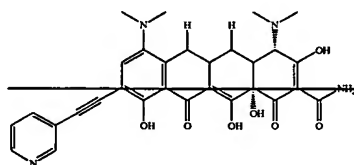
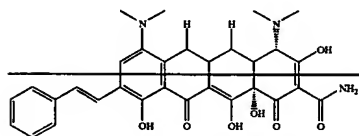
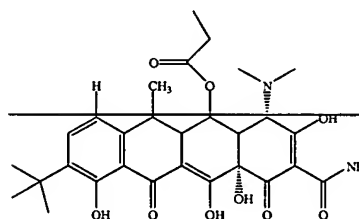
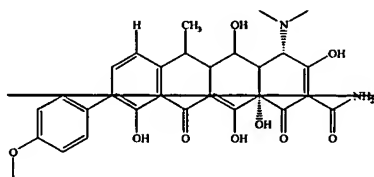
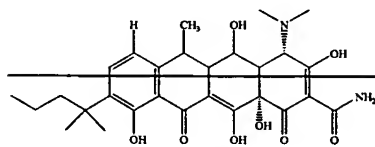
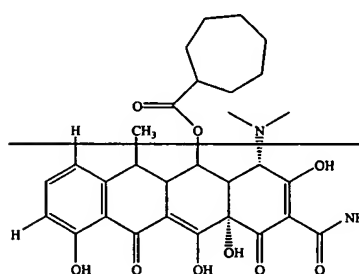
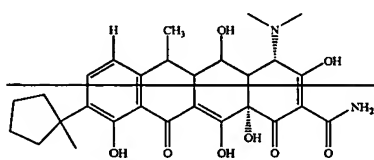
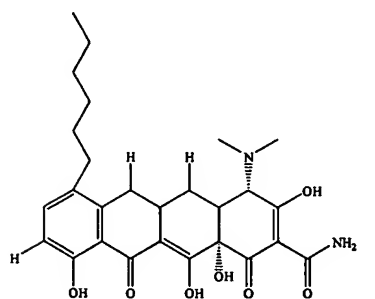
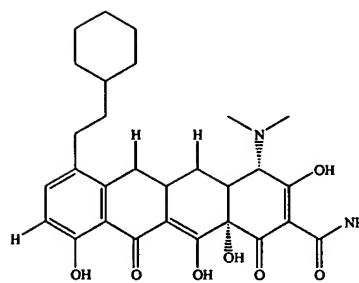
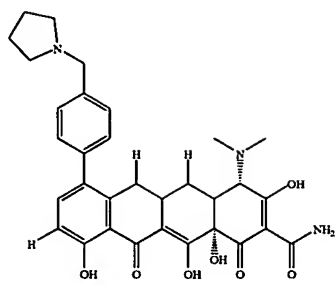
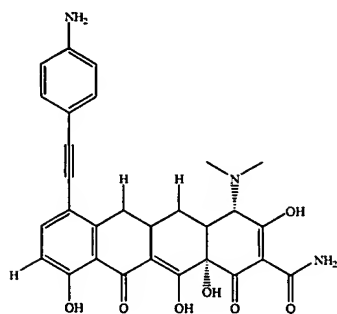
$R^9$  is ~~hydrogen, or a malaria interacting moiety;~~

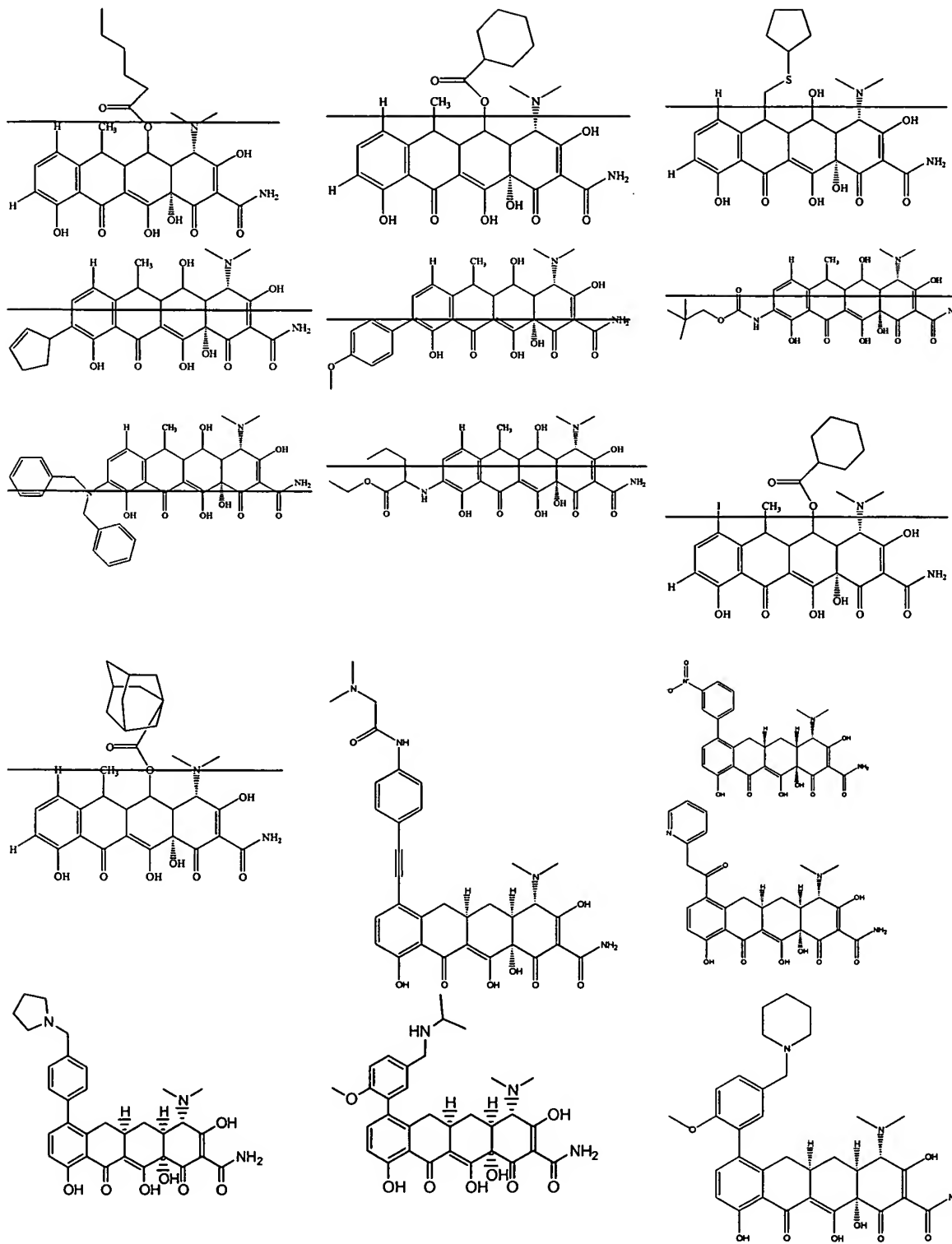
$R^8$  is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

~~with the proviso that the compound of formula I is not oxytetracycline, demeclocycline, doxycycline, chlorotetracycline, minocycline, or tetracycline; and pharmaceutically acceptable salts thereof.~~

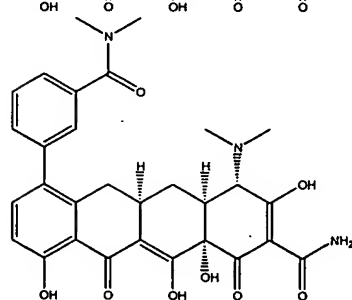
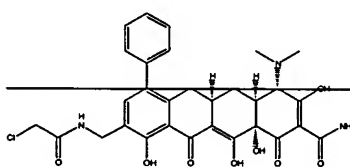
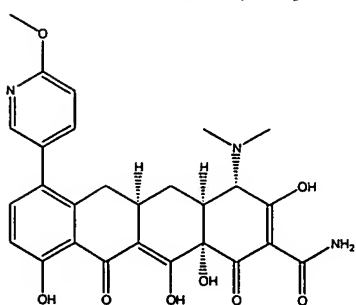
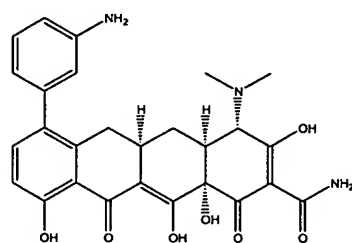
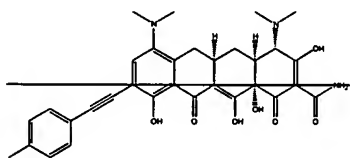
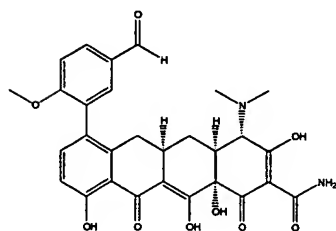
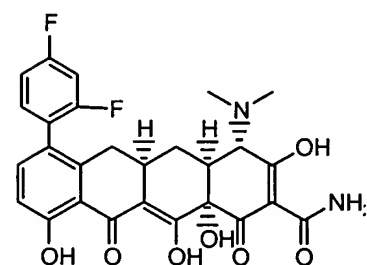
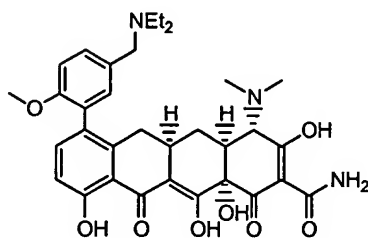
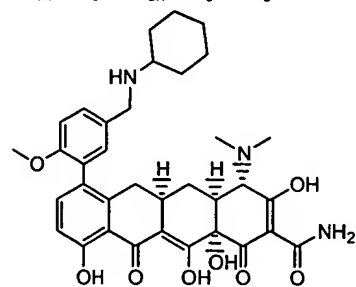
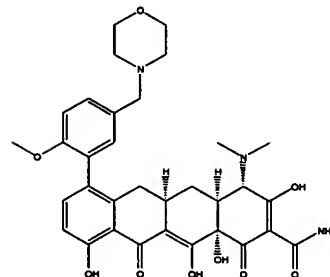
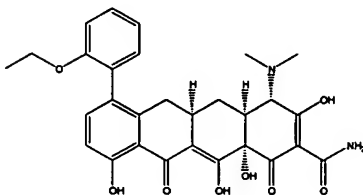
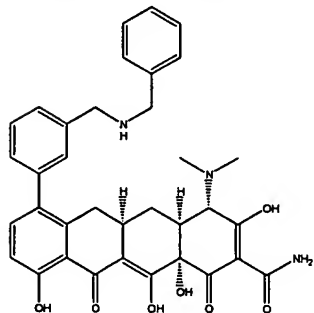
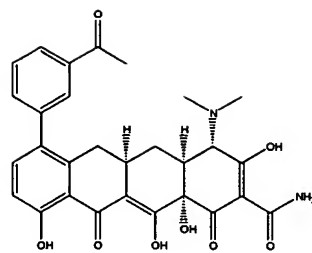
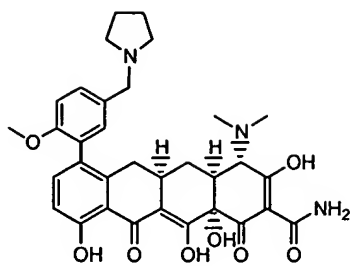
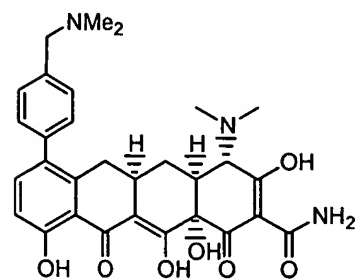
70. **(Currently Amended)** The method of claim 69, wherein said substituted tetracycline compound is selected from the group consisting of:

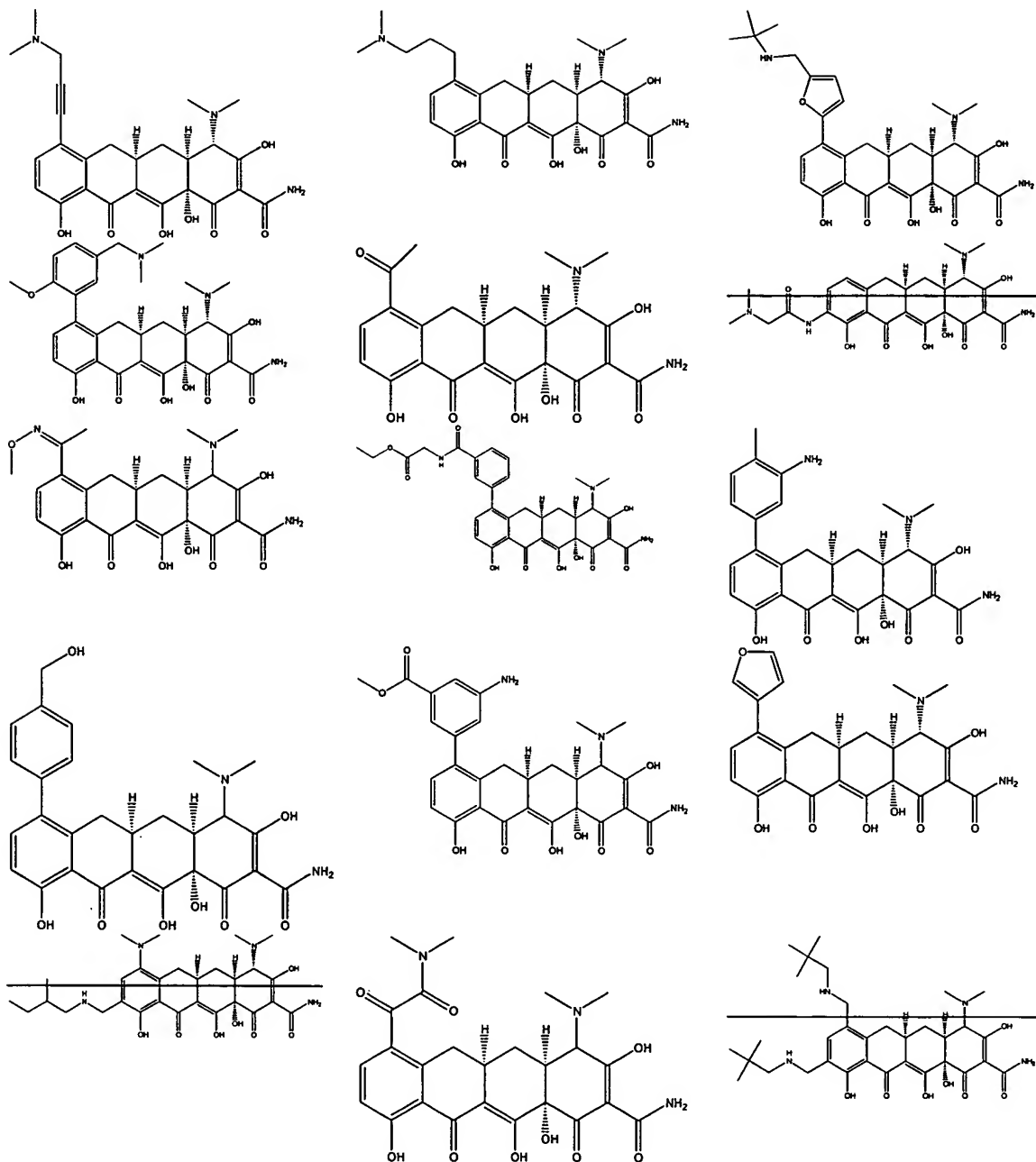


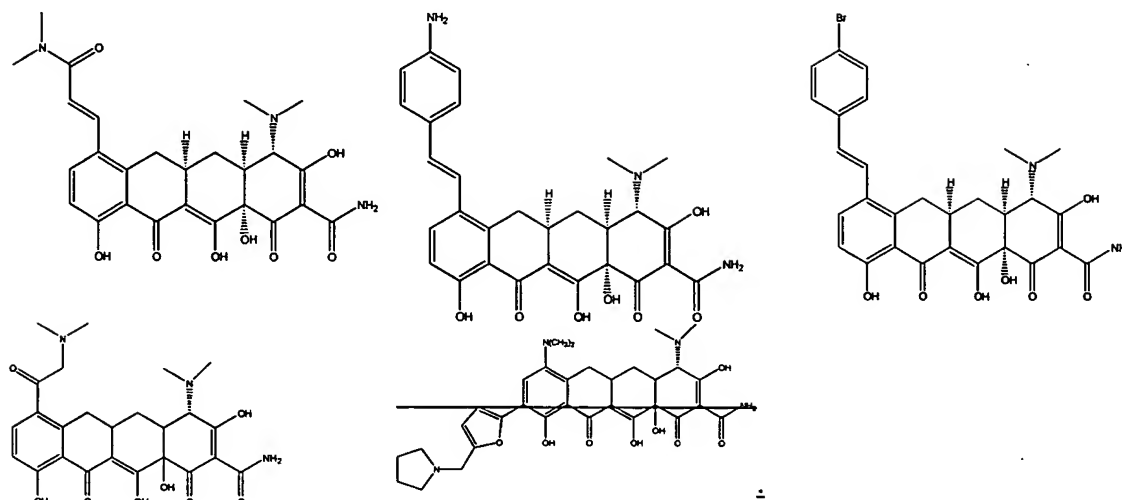












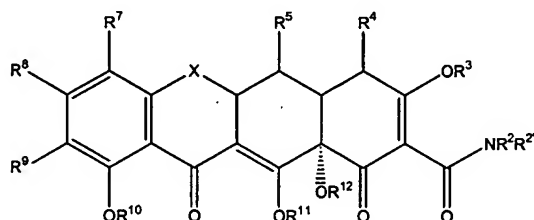
71. **(Original)** The method of claim 67 or 69, wherein said substituted tetracycline compound is a compound shown in Table 1 or Table 2.
72. **(Original)** The method of claim 67 or 69, wherein said substituted tetracycline compound is non-antibacterial.
73. **(Original)** The method of claim 67 or 69, wherein said substituted tetracycline compound is has anti-microbial gram positive activity.
74. **(Original)** The method of claim 73, wherein said anti-microbial gram positive activity is greater than about 0.05  $\mu\text{g/ml}$ .
75. **(Original)** The method of claim 74, wherein said anti-microbial gram positive activity is greater than about 5  $\mu\text{g/ml}$ .
76. **(Original)** The method of claim 75, wherein said substituted tetracycline compound has a cytotoxicity of 25  $\mu\text{g/ml}$  or greater.
77. **(Original)** The method of claim 67 or 69, wherein said substituted tetracycline compound has a MIC of 150 nM or less.

78. **(Original)** The method of claim 77, wherein said substituted tetracycline compound has a MIC of 50 nM or less.

79. **(Original)** The method of claim 78, wherein said substituted tetracycline compound has a MIC of 10 nM or less.

80. **(Original)** The method of claim 79, wherein said substituted tetracycline compound has an MIC of 5 nM or less.

81. **(Currently Amended)** A pharmaceutical composition comprising an effective amount of a substituted tetracycline compound to treat malaria in a mammal and a pharmaceutically acceptable carrier, wherein said tetracycline compound is of formula I:



(I)

wherein:

X is CR<sup>6'</sup>R<sup>6</sup>;

R<sup>2</sup>, R<sup>2'</sup>, R<sup>4'</sup>, and R<sup>4''</sup> are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R<sup>4</sup> is NR<sup>4'</sup>R<sup>4''</sup>, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R<sup>3</sup>, R<sup>11</sup> and R<sup>12</sup> are each hydrogen, or a pro-drug moiety;

R<sup>10</sup> is hydrogen, a prodrug moiety, or linked to R<sup>9</sup> to form a ring;

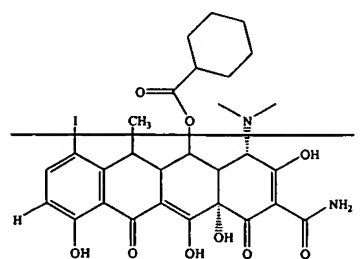
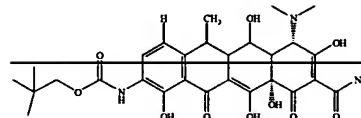
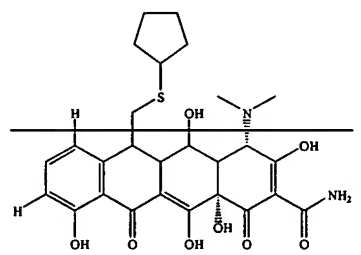
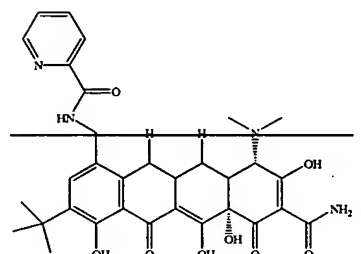
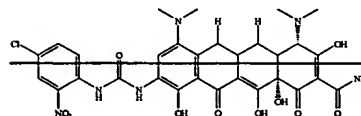
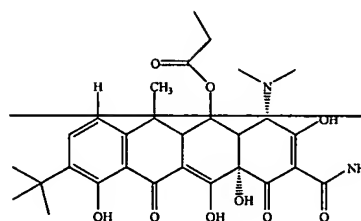
R<sup>5</sup> is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

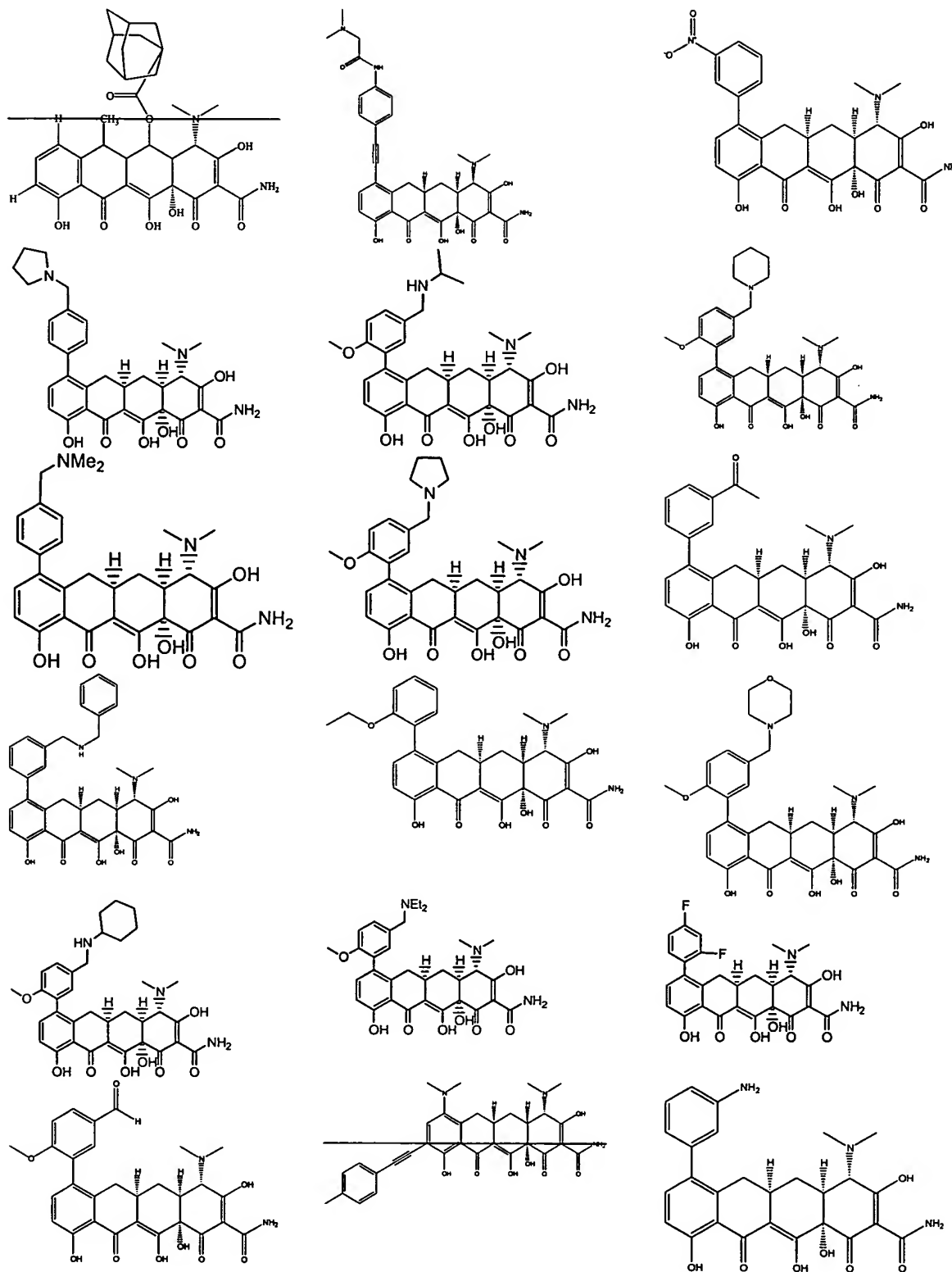
R<sup>6</sup> and R<sup>6'</sup> are independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

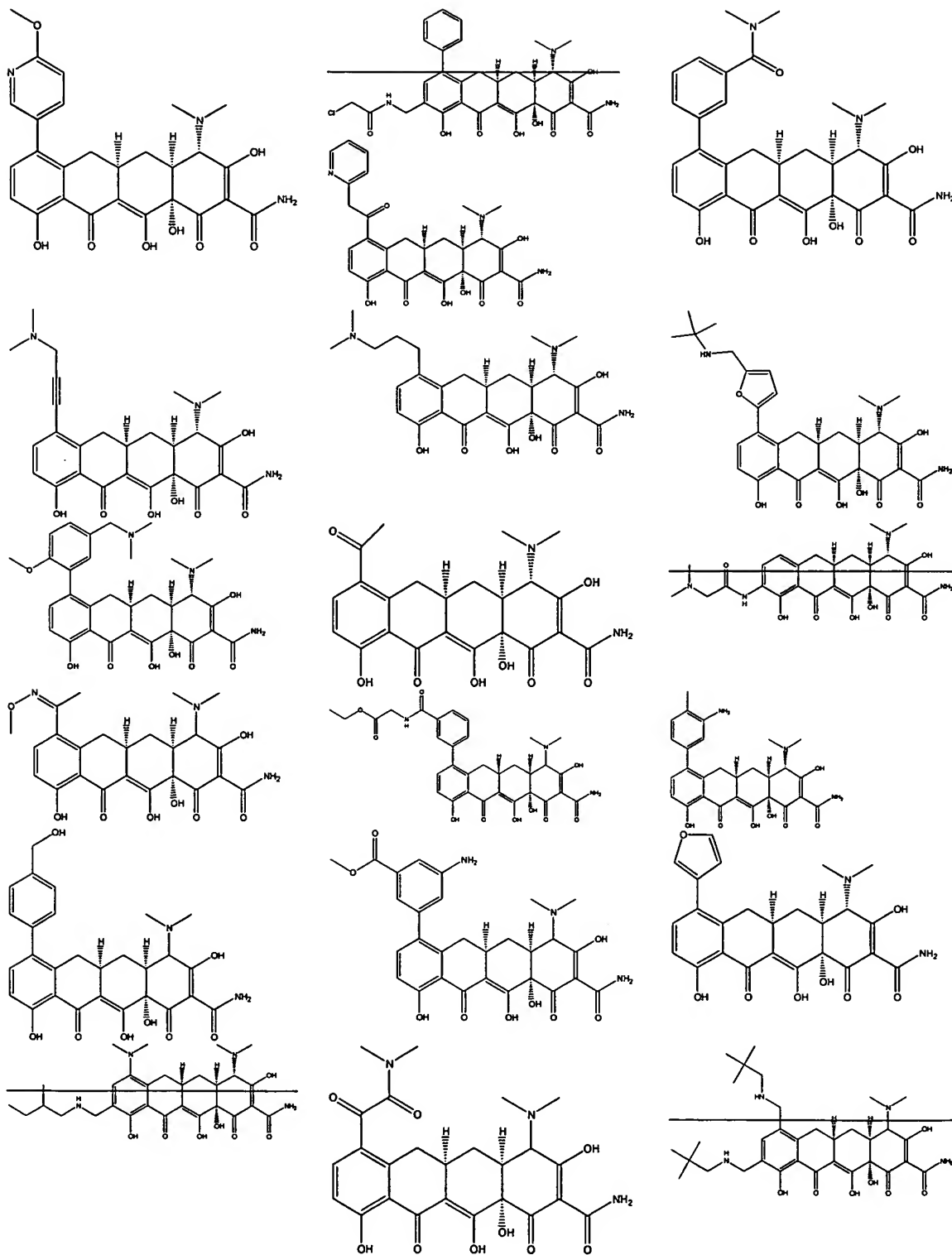
R<sup>7</sup> is hydrogen, alkylamino, dialkylamino, or a malaria interacting moiety;

R<sup>9</sup> is hydrogen, or a malaria interacting moiety;

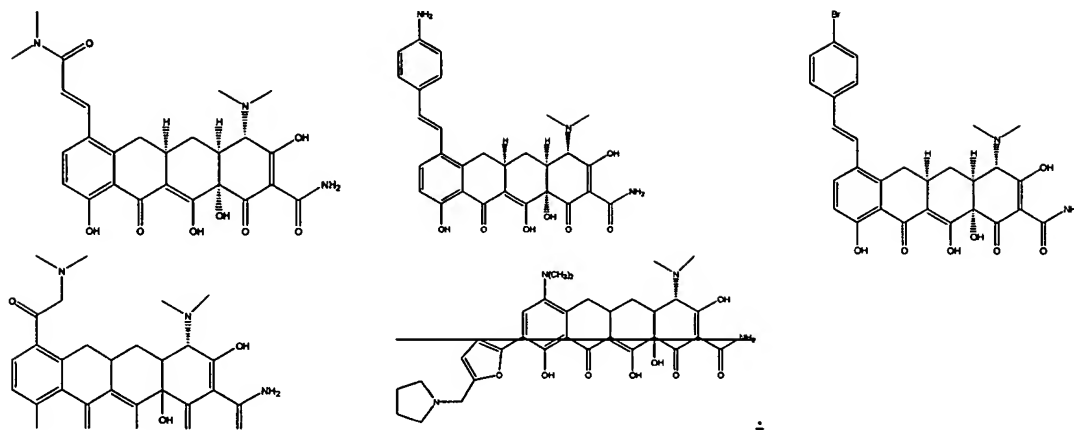
with the proviso that the compound of formula I is not oxytetracycline, demeclocycline, doxycycline, chlorotetracycline, minocycline, or tetracycline; and pharmaceutically acceptable salts thereof.











83. **(Original)** The pharmaceutical composition of claim 81, wherein said substituted tetracycline compound is a compound shown in Table 1 or Table 2.

84. **(Original)** The pharmaceutical composition of claim 81, further comprising a secondary agent.

85. **(Original)** The pharmaceutical composition of claim 84, wherein the secondary agent is selected from the group consisting of proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide and pyronaridine.

86. **(Cancelled)**

87. **(Previously Presented)** The method of claim 1, wherein the substituted tetracycline compound is

